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**IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY**

PFIZER INC.,)
PHARMACIA CORP.,)
PHARMACIA & UPJOHN INC.,)
PHARMACIA & UPJOHN COMPANY,)
G.D. SEARLE & CO.,)
G.D. SEARLE LLC,)
SEARLE LLC (DELAWARE) and)
SEARLE LLC (NEVADA))
Plaintiffs,)
v.)
TEVA PHARMACEUTICALS USA, INC.)
Defendant.)

Civil Action No: 04-754 (JCL)

**CONTAINS CONFIDENTIAL
ATTORNEYS' EYES ONLY
INFORMATION**

EXPERT REPORT OF GUENTER TRUMMLITZ, Ph.D.

I hereby submit this expert report pursuant to Fed. R. Civ. P. 26(a)(2)(B) on behalf of
Teva Pharmaceuticals USA, Inc.

I. BACKGROUND

A. Qualifications and Credentials

1. I am currently working as an independent consultant and scientific advisor in the
field of drugs known as selective inhibitors of cyclooxygenase-2 (COX-2) and in the field of

nonsteroidal anti-inflammatory drugs (NSAIDs). I also consult for Boehringer Ingelheim, a major pharmaceutical corporation, for research programs seeking new uses or treatment indications for COX-2 inhibitors. I also consult for Boehringer Ingelheim Pharma KG.

2. My expertise is based on over thirty years experience in the pharmaceutical industry in the design and development of new compounds and commercial drugs. I have participated in all phases of drug design and development, including discovery and development of lead compounds, preclinical screening, drug development and animal testing, design and regulatory approval of clinical studies, representation of clinical and other results to government regulatory agencies, management of drug design and development projects, and commercialization of a compound I invented into drugs with over a billion dollars in annual sales.

3. From 1988-2003 I was Project Leader at Dr. Karl Thomae GmbH ("Thomae"), and then International Project Leader at the Head Office of Boehringer Ingelheim GmbH.¹ Among other projects, I was responsible for the development, registration and launch of meloxicam. The meloxicam project was the first international drug development program that resulted in a worldwide launch at Boehringer Ingelheim.

4. From 1973-1988 I was Head of the Pharmaceutical Synthesis Laboratory at Thomae, and then Head of the Development Coordination Department at Thomae. I was responsible for drug design, synthesis, and preclinical testing of Thomae's drug candidate compounds ("predevelopment"), and later, project management. I was involved in synthesizing and developing drugs to be used as analgesics, anti-inflammatories, antithrombotics, gastroprotective agents, cardiovascular agents, antibiotics, antiviral agents, and as artificial sweeteners.

¹ Thomae was a subsidiary of Boehringer Ingelheim, now part of Boehringer Ingelheim Pharma KG.

5. In my business experience in drug design and development I have invented, designed, and synthesized twelve (12) compounds that were carried into the advanced development phase. These compounds were intended to treat inflammation, thrombosis, pain, ulcers, cardiovascular diseases, and as antiviral agents.

6. One of the compounds I invented is the blockbuster NSAID drug known as meloxicam. I designed the structure of the meloxicam compound and participated in its preclinical testing. Later, I was responsible for meloxicam's international clinical development, registration and worldwide launch in over one hundred (100) countries. Since 1996 meloxicam is marketed as Mobic[®], Mobec[®], Mobicox[®] and Movalis[®]. According to a Boehringer Ingelheim press conference on April 4th, 2006, worldwide sales of Mobic[®] brands exceeded US\$ 1 billion for 2005.

7. I was also involved in the invention and design of nevirapine, an antiviral anti-HIV agent which was commercialized. Nevirapine is marketed as Viramune[®].

8. I earned my Diploma in Chemistry (1969) and Ph.D. in Chemistry (1971) at the Technische Universitaet of Darmstadt. My doctoral thesis concerned the chemistry and biochemistry of polyamino-, aminoacyl-, and peptidyl-nucleoside antibiotics.

9. I was a lecturer of the FORUM Institute for Management GmbH for many years. I gave presentations and full-day workshops on international project management in drug development in Germany and other European countries.

10. I was a member of the Medicinal Chemistry Section of the American Chemical Society for many years before retirement. I am a member of the German Gesellschaft Deutscher Chemiker.

11. I have served as a reviewer for articles submitted for publication to a variety of scientific journals including the Journal of Medicinal Chemistry and the Proceedings of the National Academy of Science USA.

12. I have consulted for a number of pharmaceutical companies including Merck KG (Darmstadt), Schering AG (Berlin), and Nicox SA (France).

13. I have published over 50 articles on topics including the study of the structure and function of enzymes, synthesis and characterization of compounds that are enzyme inhibitors, design of selective inhibitors, molecular modeling approaches and drug development. I have presented over 50 scientific lectures on the pharmacology of COX-2 inhibitors, the medicinal chemistry of COX-2 inhibitors and NSAIDs, the classification and binding sites of COX-2 inhibitors and NSAIDs, the three-dimensional structure of COX isoenzymes, and on topics of drug research and development.

14. I am a co-inventor on more than 25 issued U.S. patents and more than 45 European patents. I have submitted approximately 80 patent applications concerning new pharmaceutical substances, products, and processes.

15. A copy of my curriculum vitae is attached as Exhibit A. Information regarding my compensation and prior testimony is provided in Exhibit B.

B. Compensation

16. Information about my compensation is provided in Exhibit B.

C. Prior Testimony

17. Information about my prior testimony is provided in Exhibit B.

D. Materials Reviewed

18. In addition to my own knowledge, education, and experience, I base my testimony on the materials in Exhibit C

II. SUMMARY OF OPINIONS

19. If called as a witness in this litigation, I expect to testify on the following topics which are summarized in this report:

- a. The state of the art as of November 30, 1993² of medicinal, pharmaceutical, and organic chemistry and the development and use of pharmaceutical drugs, including drugs known as enzyme inhibitors;
- b. As of November 30, 1993, the state of the art concerning compounds useful as anti-inflammatory agents, such as for the treatment of the signs and symptoms of arthritis, with the additional benefit of having significantly less harmful side effects, such as the life threatening ulcers caused by high doses of most common NSAIDs.
- c. The obviousness of the subject matter of the asserted claims of the patents-in-suit³, including objective real world evidence.
- d. I may also testify in rebuttal to testimony or opinions offered by other witnesses, in response to the opinions stated therein.
- e. I also reserve my right to supplement this report.

20. A summary of my expected testimony and the bases for that testimony is set forth in more detail below.

² My opinions are with respect to what would have been known by November 30, 1993. However, I note that my opinions would be the same with regard to June 25, 1993 or later.

³ I understand that the asserted claims of the patents in suit are claims 1-3, 7-9, 11 and 13 of U.S. Patent No. 5,466,823 ("the '823 patent"; Teva Ex. 12), claims 1-5 and 15-18 of U.S. Patent No. 5,563,165 ("the '165 patent"; Teva Ex. 33"), and claims 1-4 and 11-17 of U.S. Patent No. 5,760,068 ("the '068 patent"; Teva Ex. 8).

III. BACKGROUND ON INHIBITORS OF CYCLOOXYGENASE

A. The Role of Inflammation in Rheumatic Disease

21. Rheumatic diseases are connective tissue diseases which involve inflammation of joint tissue. Rheumatic diseases include, among others, osteoarthritis, rheumatoid arthritis, ankylosing spondylitis, and gout.

22. The inflammation of joint tissue in rheumatic disease can be ameliorated by anti-inflammatory drugs. NSAIDs are one type of anti-inflammatory drug. NSAIDs relieve the symptoms caused by inflammation, but do not cure or prevent rheumatic disease. NSAIDs are the main therapy for symptomatic pain relief for rheumatic diseases.

23. NSAIDs provide anti-inflammatory, analgesic, and antipyretic therapy. It has been known since 1971 that NSAIDs act by inhibiting prostaglandin⁴ biosynthesis in the cells of the body. Prostaglandins are involved in the inflammation process.

24. Prostaglandins are produced by an enzyme called prostaglandin synthase.⁵ In the first step of prostaglandin synthesis a portion of the prostaglandin synthase enzyme named cyclooxygenase (COX) enzyme transforms arachidonic acid⁶ into prostaglandin PG₂.⁷ By blocking the action of the COX enzyme, and thereby reducing the production of prostaglandins, NSAIDs can reduce inflammation, provide an analgesic effect, and reduce fever.

25. In addition to their use as anti-inflammatory agents in arthritis, NSAIDs are also used for acute pain from, for example, headaches, dysmenorrhea, or sports injuries.

⁴ J. R. Vane, "Inhibition of prostaglandin synthesis as a mechanism of action of aspirin-like drugs," 231 Nature (New Biol) 232-35 (1971).

⁵ W. L. Smith, D. L. DeWitt, R. M. Garavito, "Cyclooxygenases: Structural, Cellular, and Molecular Biology," 69 Ann. Rev. Biochem. 145-82 (2000).

⁶ Arachidonic acid is the main starting material of prostaglandin biosynthesis and is produced by the enzyme phospholipase from phospholipids.

⁷ Prostaglandin PG₂ is later transformed to prostaglandin PGH₂ which, in turn, is transformed into the regulator compounds such as prostaglandin E₂ (PGE₂), prostacyclin (PGI₂), and thromboxane (TXA₂). These regulators are involved in inflammation, blood clotting, and many other processes.

B. The Chemical Structure of NSAIDs

26. NSAIDs are COX inhibitors. NSAIDs can be classified based on the pharmacophore⁸ they contain. One classification of COX inhibitor pharmacophores known in 1993 is as follows:⁹

- Substituted diphenyl-heterocycle compounds which today are called “coxibs.” A DuPont compound known as DuP-697 and a Searle compound known as SC-58125 were among the first example compounds of this class. In 1999, rofecoxib and celecoxib were the first compounds of this class to be commercialized.¹⁰ A precursor of this class was flumizole.¹¹
- Enolcarboxamide compounds known as “oxicams.” Examples are meloxicam and piroxicam. Meloxicam was the first drug specifically launched as a “COX-2 selective inhibitor” in Europe, Asia, Africa, and South America. These launches occurred in 1995-97. Meloxicam was launched in the United States as an NSAID in 2000.
- Sulfanilide compounds known as “sulides.” Examples are nimesulide, flosulide and NS-398.
- Aryl- and heteroaryl acetic acid and propionic acid compounds which include the subclasses “fenacs” and “profens.” Examples are indomethacin, naproxen, ibuprofen, diclofenac, oxaprozin, and many others.¹²
- Anthranilic acid compounds known as “fenamates.”
- Pyrazolone compounds, a small class based on the compound phenylbutazone.
- Salicylic acids, such as acetylsalicylic acid, which is also called aspirin.

⁸ A pharmacophore is a set of structural elements common to group of compounds which is essential for their pharmacological activity.

⁹ See, e.g., G. Trummelitz and J. van Ryn, “Designing selective COX-2 inhibitors: Molecular Modeling Approaches,” 5 *Current Opinion in Drug Discovery & Development* 550-61 (2002); Fig 4 p. 58.

¹⁰ Rofecoxib was first launched in March 1999 in Mexico and celecoxib was first launched in the US in February 1999.

¹¹ E. H. Wiseman, H. M. McIlhenny, J. W. Bettis, “Flumizole, a New Nonsteroidal Anti-Inflammatory Agent,” 64 *J. Pharmaceutical Sci.* 1469-75 (1975).

¹² “Lumiracoxib,” developed after 1993, is in this category even though it does not have the pharmacophore of the other “coxibs.” Lumiracoxib shows that generic drug names are not necessarily representative of their pharmacophore.

27. Celecoxib belongs to the NSAID class known as “coxibs” having the pharmacophore I call a “substituted diphenyl-heterocycle.”

28. The substituted diphenyl-heterocycle pharmacophore differs from the other classes listed above because the substituted diphenyl-heterocycle pharmacophore: (1) does not contain an acidic group as a necessary part of the pharmacophore; and (2) encompasses neutral compounds. For example, meloxicam has an acidic enol-carboxamide group and nimesulide has a weakly acidic alkyl-sulfonanilide.

29. In each of the classes of compounds I listed above as “COX Inhibitor Pharmacophores Known in 1993,” except for pyrazolone,¹³ there is at least one compound now known to be more active towards COX-2 than COX-1, some of which have been commercialized. Some of these, such as nimesulide, were commercialized before COX-2 was discovered. My compound, meloxicam, is more active towards COX-2 than COX-1 and was already in advanced development in 1991 when the existence of COX-2 was confirmed.

30. The diversity in the structures of NSAID pharmacophores reflects the fact that while they all bind to the active site of COX enzymes, called the “COX channel,” different binding sites are involved within that channel for each pharmacophore.¹⁴ For example, each of the “coxibs” interacts with the same binding site within the COX channel, but it is a different binding site than that of the other classes of NSAIDs.

31. In general, it is not necessary to know the nature or structure of the binding site to develop a drug in a particular class because preclinical screening of drug compounds can be

¹³ Very few compounds were made in this class and little data is available.

¹⁴ The enzyme prostaglandin H synthase (PGHS) has two active sites: a peroxidase site and a cyclooxygenase (COX) site. The coxib drugs bind to the COX site of PGHS. By about 1991, the name “cyclooxygenase enzyme” became popular for PGHS and the inhibitors of this enzyme were called “COX inhibitors.”

accomplished without that information.¹⁵ In drug design and development, the differences between pharmacophores are inferred from the differences in their chemical structures.

IV. LEVEL OF SKILL AND KNOWLEDGE IN THE ART

A. Experience And Training Of A Person Of Ordinary Skill In The Art

32. As of November 30, 1993, a person of ordinary skill in the art to which the asserted claims of the patents in suit pertain would have a Ph.D. in medicinal chemistry, or a related field. In addition, the person of ordinary skill in the art would have learned about patent protection of pharmaceuticals. The person of ordinary skill would have engaged in extensive teamwork and collaboration with professionals in various disciplines and through that experience and training have become knowledgeable in other fields such as biochemistry, pharmacology, and clinical studies, among others.¹⁶ For example, my meloxicam research team included medicinal chemists, pharmacologists, an M.D. clinician, and others involved in drug formulation, pharmacokinetics, and toxicology who would participate from time to time.

33. I understand that the hypothetical person of ordinary skill in the art would be aware of all publications and prior art pertinent to the research goal and problem to be solved.

B. General Knowledge Of A Person Of Ordinary Skill In The Art

34. By November 30, 1993 a person of ordinary skill in the art would have known about the Keystone conference, a significant conference involving leaders in the field of anti-inflammatory agents, including COX inhibitors, held in January, 1992 in Keystone, Colorado. At the Keystone conference, DuPont scientists made significant disclosures concerning COX

¹⁵ For example, pharmacologically active substituted diphenyl-heterocycle compounds were developed before 1993 without structural characterization of the binding site.

¹⁶ See, e.g., Daniel Lednicer, Series Preface, pp. xi-xiii, "Nonsteroidal Anti-inflammatory Drugs," ed. by Joseph G. Lombardino (1985) (Exhibit A, attached).

inhibitors and the compound DuP-697 which I describe in detail below. These disclosures generated great interest in COX-2 selective inhibitors.¹⁷

C. Companies Working On Cox-2 Selective Inhibitors In 1993

35. In November, 1993 it was widely known that various companies were working to develop selective COX enzyme inhibitors, including Merck Frosst Canada, Inc. ("Merck Frosst"), G. D. Searle & Co. ("Searle"), and E. I. du Pont de Nemours & Co. ("DuPont").

36. In addition, in 1989 Ciba-Geigy published about a compound called flosulide (CGP 28238) which was suggested to have improved gastrointestinal safety.¹⁸ Flosulide has the sulide pharmacophore.

37. Another compound known in 1993 having the sulide pharmacophore was Taisho's NS-398. In 1993, NS-398 was reported to be COX-2 selective.¹⁹ As far as I know, neither flosulide nor NS-398 was commercialized.

V. BOEHRINGER INGELHEIM'S MELOXICAM WAS THE FIRST COMPOUND LAUNCHED AS A SELECTIVE COX-2 INHIBITOR

A. Meloxicam Was Developed Before The Discovery Of COX-2

38. At Boehringer Ingelheim, we focused on the oxicam class of NSAIDs. My compound, meloxicam, was developed before the discovery of COX-2 and became the leader in this class at Boehringer Ingelheim. In mid-1993 Boehringer Ingelheim decided to submit the meloxicam dossier of international registration to the health authorities. In February, 1994, the first meloxicam submission for approval was performed in France.

¹⁷ See P. Prasit, D. Riendeau, and C. C. Chan, "Discovery of Vioxx (rofecoxib)," Ch. 3 in "Therapeutic Roles Of Selective COX-2 Inhibitors," ed. by JR Vane (2001), at pp. 66-67.

¹⁸ I. Wiesenberger-Boettcher et al., "The Pharmacological Profile of CGP 28238, A Novel Highly Potent Anti-inflammatory Compound," 15 *Drugs Exptl. Clin. Res.* 501-09 (1989).

¹⁹ Futaki et al., Abstract 154, World Congress Inflammation '93, Vienna, October 10-15, 1993.

B. Testing Proved That Meloxicam Was COX-2 Selective

39. After the disclosure of the second COX gene in 1991, I was interested in determining the COX-2 selectivity of meloxicam. Boehringer Ingelheim had been developing a guinea pig macrophage whole cell system in about 1989-93 as a model for inflammation cells.²⁰ By the middle of 1993, we had tested meloxicam in this model and found that it was a COX-2 selective inhibitor.

40. In 1993-94, Professor Vane confirmed the COX-2 selectivity of meloxicam using the LPS-stimulated mouse macrophage assay for COX-2 and bovine aortic endothelial cell assay for COX-1.²¹

41. In 1994 I had meloxicam tested in Boehringer Ingelheim's established human recombinant COX-1 and COX-2 enzyme assays, both whole cell and microsomal preparations.²² Again, meloxicam was COX-2 selective.

42. When Searle disclosed the compound SC-58125,²³ I expected SC-58125 to be COX-2 selective. I made a sample of SC-58125 and compared the selectivity of SC-58125 to meloxicam using a whole blood assay²⁴ and found them both to be COX-2 selective.

43. In addition, meloxicam has been tested for COX-2 selectivity in many newer systems. All of these test systems provide a measure of the COX-2 selectivity and can be used

²⁰ For the assay, see G. Engelhardt, R. Bogel, C. Schnitzer, and R. Utzmann, "Meloxicam: Influence on Arachidonic Acid Metabolism," 51 *Biochemical Pharmacology* 21-28 (1996).

²¹ For the assay, see J. A. Mitchell et al., "Selectivity of nonsteroidal anti-inflammatory drugs as inhibitors of constitutive and inducible cyclooxygenase," 90 *Proc. Nat'l Acad. Sci.* 11693-97 (1993).

²² For the assay, see L. Churchill et al., "Selective inhibition of human cyclo-oxygenase-2 by meloxicam," 4 *Inflammopharmacology* 125-35 (1996).

²³ See K. Seibert et al., 91 *Proc. Nat'l Acad. Sci. USA* 12013-17 (1994).

²⁴ For the assay, see P. Patrignani et al., "Biochemical and pharmacological characterization of the cyclooxygenase activity of human blood prostaglandin endoperoxide synthases," 271 *J. Pharmacol. Exp. Ther.* 1705-10 (1994).

for screening and/or profiling compounds. Each of these test systems has its merits as discussed in a review article by Pairet.²⁵

C. Knowledge Of Other COX-2 Selective Compounds

44. As part of my job, both in research and development, and as a project manager, it has always been an important regular task for me to watch for developments in competitor's compounds and pharmacophores.

45. As of November 30, 1993, I was not aware of any commercial anti-inflammatory compounds having a diaryl-heterocycle structure.

46. After the Keystone conference, the properties of the compound DuP-697 suggested to a person of ordinary skill in the art that a new pharmacophore might be found based on a substituted diphenyl-heterocycle structure, where substitution of a methylsulfonyl on one of the phenyl groups was a key component. This was confirmed in Merck Frosst's U.S. Application No. 08/082,196 ("the Merck '196 application"), filed June 24, 1993, which discloses COX-2 selective compounds belonging to this substituted diphenyl heterocycle pharmacophore.

47. As set forth above, in 1993, I understood that meloxicam was a selective COX-2 inhibitor. I also knew that Boehringer Ingelheim would be (and ultimately was) the first to market a compound as a selective COX-2 inhibitor, namely meloxicam.

48. Upon seeing the publication of Searle's SC-58125,²⁶ I became convinced that Searle intended to commercialize a compound of the substituted diphenyl-heterocycle pharmacophore. By that time, I was already preparing for the launch of meloxicam to be marketed as the first

²⁵ M. Pairet and J. van Ryn, "Experimental Models used to investigate the differential inhibition of cyclooxygenase-1 and cyclooxygenase-2 by non-steroidal anti-inflammatory drugs," 47 (Suppl 2) *Inflamm. Res.* S93-S101 (1998).

²⁶ See K. Seibert et al. (1994), above.

COX-2 selective compound in Europe. Therefore, I was not interested in pursuing the substituted diphenyl-heterocycle pharmacophore.

VI. THE PROBLEM—GASTROINTESTINAL SIDE EFFECTS OF NSAID USE

A. Side Effects Of NSAIDs Caused Many Deaths

49. Serious adverse reactions to use of NSAIDs include gastric erosions, peptic ulcers and perforations, and upper and lower gastrointestinal hemorrhages. These serious side effects cause many hospitalizations and deaths. By 1991, thousands of deaths annually were attributed to the side effects of NSAID use.²⁷

50. Adverse reactions to NSAIDs were a topic of great concern by 1990 and were the main factor motivating further research to improve NSAIDs. The goal of most research programs in the NSAID field by 1990 was to reduce gastrointestinal side effects and improve drug safety. Improving efficacy was not a main concern.

51. Thus, by 1990, the problem motivating the design and development of new NSAIDs was the need for compounds useful as anti-inflammatory agents, such as for the treatment of arthritis, with the additional benefit of having significantly less harmful side effects, such as the life threatening ulcers associated with the use of high doses of most common NSAIDs.

B. Knowledge of COX-1 and COX-2 Isoforms

52. Since the demonstration by Vane that the mechanism of action of aspirin and other NSAIDs is the inhibition of prostaglandin synthesis through blockade of cyclooxygenase (COX), it has been widely accepted that the mechanisms of action for both the therapeutic action and the side effects of NSAIDs are closely related.

²⁷ Fries JF, Miller SR, Spitz PW, Williams CA, Hubert HB, Bloch DA. "Toward an epidemiology of gastropathy associated with nonsteroidal anti-inflammatory drug use." 96 *Gastroenterology* 647-55 (1989); Fries JF, Williams CA, Bloch DA, Michel BA. "Nonsteroidal anti-inflammatory drug-associated gastropathy: incidence and risk factor models." 91 *Am J Med* 213-22 (1991).

53. Analysis of the pharmacological effects of NSAIDs in different cells and of the severity of toxic effects of different NSAIDs led to the belief in the existence of more than one form of the COX enzyme.

54. The existence of different forms of an enzyme, called “isoforms” or “isoenzymes,” was known to occur for enzymes other than COX. For example, nitric oxide synthase (NOS) enzyme was known to have “constitutive” and “inducible” forms.²⁸ The constitutive form is normally present in certain tissues, for example vascular tissue, and produces nitric oxide in response to physiological stimuli, while the other form is induced by cytokines after activation of macrophages under certain conditions.

55. Likewise, for the COX enzyme it was believed that constitutive and inducible forms might exist because it was known that inflammation involves processes which induce biosynthesis of various mediators such as prostaglandins. Blocking production of an inducible form of COX was therefore expected to have an anti-inflammatory effect. However, blocking production of the constitutive form which is necessary for physiological functions²⁹ might result in unwanted side effects.

56. As early as 1972, Flower and Vane suggested that acetaminophen exerted an antipyretic effect by inhibition of a distinct isoform of COX in brain tissue.³⁰

57. Moreover, in 1988 it was shown that, in spite of treatment with antibodies raised against COX, fibroblasts were still able to increase their prostaglandin biosynthesis activity in

²⁸ S. Moncada et al, “Nitric Oxide: Physiology, Pathophysiology, and Pharmacology,” 43 *Pharmacological Reviews* 109-142, 133 (1991).

²⁹ COX enzymes were known to be present in cells of the gastric mucosa, platelets, vascular endothelium, and others. See Peter H. Nelson, “Cyclooxygenase Inhibitors,” Vol. II *CRC Handbook of Eicosanoids: Prostaglandins and Related Lipids* 59-133 (A.L. Willis ed., 1989).

³⁰ R.J. Flower and J. R. Vane, “Inhibition of prostaglandin synthetase in brain explains the antipyretic activity of paracetamol (4-acetamidophenol),” 240 *Nature* 410-11 (1972).

response to stimulus. This increased prostaglandin biosynthesis was believed to be due to an *inducible* COX isoform.³¹

58. Similarly, prostaglandin synthesis was shown to be strongly stimulated by bacterial endotoxin in human monocytes *in vitro*³² as well as mouse macrophages *in vivo*.³³ This increase in prostaglandin synthesis was associated with *de novo* synthesis of induced COX protein.³⁴

59. Studies in the rat ovary also provided evidence that two distinct forms of COX exist and that one of these two forms can be selectively regulated by hormones.³⁵ The existence of an inducible COX was also indicated in tracheal cells.³⁶

60. In 1991, a second gene responsible for expression of a COX isoform was discovered by Xie et al,³⁷ Kujubu et al,³⁸ and O'Banion et al.³⁹ This confirmed the existence of an inducible COX isoform. Thereafter, the two COX isoforms were called COX-1, the constitutive isoform, and COX-2, the inducible isoform.

³¹ A. Raz, A. Wyche, N. Siegel, and P. Needleman, "Regulation of fibroblast cyclooxygenase synthesis by interleukin-1," 263 J. Biol. Chem. 3022-25 (1988); A. Raz, A. Wyche, and P. Needleman, "Temporal and pharmacological division of fibroblast cyclooxygenase expression into transcriptional and translation phases," 86 Proc. Natl. Acad. Sci. USA 1657-61 (1989).

³² J. Y. Fu, J. L. Masferrer, K. Seibert, A. Raz, P. Needleman, 265 J. Biol. Chem. 16737-40 (1990).

³³ J. L. Masferrer, B. S. Zweifel, K. Seibert, P. Needleman, "Selective regulation of cellular cyclooxygenase by dexamethasone enzyme and endotoxin in mice," 86 J. Clin. Invest. 1375-79 (1990).

³⁴ *Id.*; J. L. Masferrer, K. Seibert, B. S. Zweifel, P. Needleman, "Endogenous glucocorticoids regulate an inducible cyclooxygenase enzyme," 89 Proc. Natl. Acad. Sci. USA 1375-21 (1992).

³⁵ W. Y. L. Wong, D. L. DeWitt, W. L. Smith, J. S. Richards, "Rapid induction of prostaglandin endoperoxide synthetase induced by luteinizing hormone and cAMP is blocked by inhibitors of transcription and translation," 3 Mol. Endocrinol. 1714-23 (1989); W. Y. L. Wong, J. S. Richards, "Evidence for two antigenically distinct molecular weight variants of prostaglandin H synthase in rat ovary," 5 Mol. Endocrinol. 1269-79 (1991).

³⁶ G. D. Rosen, T. M. Birkenmeier, A. Raz, M. J. Holtzmann, "Identification of cyclooxygenase-related gene and its potential role in prostaglandin formation, 164 Biochem. Biophys. Res. Commun. 1358-65 (1989).

³⁷ W. Xie, J. G. Chipman, D. L. Robertson, R. L. Erikson, D. L. Simmons, "Expression of a mitogen-responsive gene encoding prostaglandin synthase is regulated by mRNA splicing," 88 Proc. Natl. Acad. Sci. USA. 1692-96 (1991).

³⁸ D. A. Kujubu, B. S. Fletcher, B. C. Varnum, R. W. Lim, H. R. Herschmann, "TIS10, a phorbol ester tumor promotor-inducible mRNA from Swiss 3T3 cells, encodes a novel prostaglandin synthase, cyclooxygenase homologue," 266 J. Biol. Chem. 12866-72 (1991).

³⁹ M. K. O'Banion, V. D. Winn, D. A. Young, "cDNA cloning and functional activity of a glucocorticoid-regulated inflammatory cyclooxygenase," 89 Proc. Nat'l Acad. Sci. 4888-92 (1992).

61. Discover of the gene responsible for COX-2 expression made it possible for every researcher in the field to clone the gene to prepare an *in vitro* enzyme assay to screen compounds for activity towards COX-1 and COX-2 separately.⁴⁰ Many companies did so and these test systems were published in 1994 and later.⁴¹

VII. THE HYPOTHESIS—COX-2 SELECTIVE INHIBITORS WILL REDUCE GASTROINTESTINAL SIDE EFFECTS

62. A person of ordinary skill in the art as of November, 30, 1993, would have been motivated to solve the problem caused by the severe gastrointestinal side effects of NSAIDs. As I describe below, since 1991, when the existence of COX-2 was confirmed, it was the widely accepted hypothesis in the art that the solution to the problem of gastrointestinal side effects of NSAIDs was to develop a compound that would selectively inhibit COX-2 without inhibiting COX-1.

VIII. DEMONSTRATION OF THE SOLUTION TO THE PROBLEM BY MERCK FROSST

63. In June 1993, scientists at Merck Frosst filed a patent application for new anti-inflammatory compounds having the property of “COX-2 selectivity.” The “COX-2 selectivity” of the Merck Frosst compounds in terms of the ratio of $IC_{50}(COX-1):IC_{50}(COX-2)$ was over 100.⁴² The example compounds of the Merck ‘196 application were a solution to the problem of gastrointestinal side effects of NSAIDs.⁴³

⁴⁰ Nielson, K and Hla, T., “Human cyclooxygenase-2 cDNA,” 89 Proceedings of the National Academy of Sciences 7384-88 (August, 1992).

⁴¹ See Pairet and van Ryn, above.

⁴² See U.S. Application No. 08/082,196 (“the ‘196 application”), filed June 24, 1993, page 12, lines 2-4. U.S. Patent No. 5,474,995 (“the ‘995 patent”) issued on December 12, 1995 as a continuation-in-part of the ‘196 application. I understand from Teva’s attorneys that the ‘995 patent is prior art to celecoxib for the subject matter contained within the ‘196 application.

⁴³ In this report I refer only to the beliefs, motivations, and experimental results of workers in the field up to November 30, 1993 as they would have been understood by a person of ordinary skill in the art. Whether or not

64. The Merck '196 application is the only reference of which I am aware that (a) is dated before November 30, 1993, (b) discloses a group of numerous COX-2 selective inhibitors which are anti-inflammatory, and (c) explicitly provides that the compounds are more active towards COX-2 than COX-1, based on *in vitro* IC₅₀ activities where the compounds are "more than 100 times more effective in inhibiting COX-2 than they are at inhibiting COX-1."⁴⁴

65. The Merck '196 application solved the problem of the life-threatening ulcers associated with high doses of most common NSAIDs. The Merck '196 application also taught a pharmacophore that can be used to develop new compounds that would be expected to be COX-2 selective and solve that problem. Therefore, a person of ordinary skill in the art as of November 30, 1993 would have certainly started with the Merck '196 application when trying to design and develop new COX-2 selective inhibitors.

A. The COX-2 Selective Pharmacophore Is Learned From The Example Compounds And Data In The Merck '196 Application

66. The Merck '196 application teaches a COX-2 selective pharmacophore. This teaching is taken from the examples compounds and *in vitro* biological data presented.

67. The example compounds are in Tables I and II on pages 32-43. These compounds teach a person of ordinary skill in the art a pharmacophore that can be followed to make compounds reasonably expected to be COX-2 selective.

68. The *in vitro* biological data of the Merck '196 application would have been useful to a person of ordinary skill in the art in 1993 because they are consistent with the COX-2 selectivity of example compounds. The biological data of the Merck '196 application would also

actual COX-2 selectivity has been demonstrated today in a clinical setting, and whether or not COX-2 selectivity has actually been shown to be the cause of reduced gastrointestinal side effects in human clinical trials are beyond the scope of this report.

⁴⁴ '196 application, page 12, ll. 3-4.

have been used by competitors to select a compound to synthesize for comparative testing against other compounds. This comparative testing is an essential part of a drug project.

69. In view of the Merck '196 application, a competitor would be motivated to make a series of compounds based on the new pharmacophore and other prior art knowledge, with a reasonable expectation that those compounds would be COX-2 selective. The competitor would then compare the results for this series of compounds to selected example compounds of the Merck '196 application.

70. In contrast, U.S. Patent No. 5,466,823⁴⁵ ("the '823 patent") and U.S. Patent No. 5,563,165⁴⁶ ("the '165 patent"), two of the patents in suit, lack such *in vitro* biological data. Therefore, a person of ordinary skill in the art would have no data to confirm the COX-2 selectivity of any compound of the '823 and '165 patents in suit. Further, there would be no data to motivate the choice of a compound to synthesize for comparative testing.

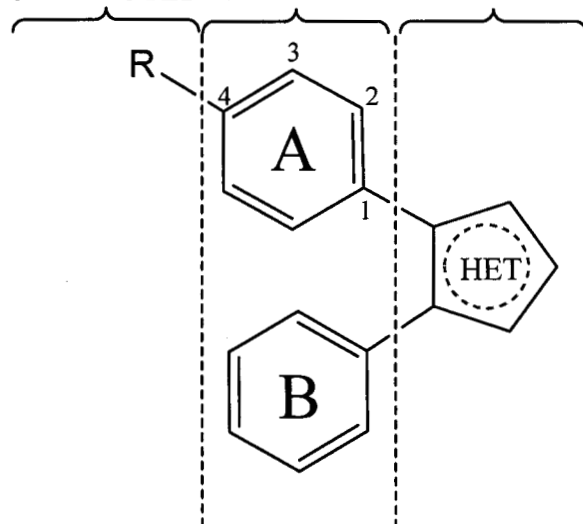
B. The Substituted Diphenyl-Heterocycle Pharmacophore Disclosed By Merck Frosst

71. The pharmacophore taught by the Merck '196 application is a substituted diphenyl-heterocycle having the structure shown below:

⁴⁵ Teva Ex. 12.

⁴⁶ Teva Ex. 33.

SUBSTITUTED DIPHENYL HETEROCYCLE



72. In this pharmacophore, R is a sulfamyl (SO_2NH_2) or methylsulfonyl substituent (SO_2CH_3) located at the 4-position of one of the phenyl rings. “HET” refers to a heterocycle and the phenyl rings are labeled “A” and “B” for ease of reference.

73. The substituted diphenyl-heterocycle pharmacophore disclosed by Merck Frosst has three rings—a central five-membered heterocyclic ring which is attached to two six-membered phenyl rings. The phenyl groups are attached to the heterocyclic ring on adjacent atoms of the heterocyclic ring. In organic chemistry, this adjacent substitution is called “vicinal” substitution of the heterocycle.

74. The five-membered ring is heterocyclic. This means that one or more of its five atoms are nitrogen, oxygen, or sulfur, rather than carbon. Further, the five-membered heterocyclic ring can have “shared” electrons which contribute to the binding between its atoms. The “shared” electrons are represented by the dotted circle in the figure above.⁴⁷ The heterocycle is planar because it contains double bonds.

⁴⁷ A heterocycle may have one or more double bonds which represent electrons that may be shared between atoms of the ring, or a heteroatom may have an electron pair that is “shared” with other atoms in the heterocycle.

75. The heterocycle acts as a scaffold holding the two phenyls in place. The size and shape of the heterocycle is not much affected by the identity and position of its heteroatoms. In the pharmaceutical arts, medicinal chemists often replace a heterocycle with another heterocycle of the same size and shape when synthesizing compounds expected to have similar biological properties.

76. A sulfamyl substituent on the pharmacophore would be useful because of its affect on bioavailability. The lipophilicity of diphenyl-heterocycle compounds was known to be high, which in general reduces bioavailability. Replacing a methylsulfonyl substituent by a sulfamyl substituent in the pharmacophore would reduce the lipophilicity of a compound.⁴⁸ The bioavailability of a compound having too high a log P would be increased by reducing its log P.⁴⁹

77. A sulfamyl substituent on the pharmacophore would also be useful because it can be used to make prodrugs. For example, acylsulfonamide has been used to make a prodrug.⁵⁰

IX. CELECOXIB WOULD HAVE BEEN OBVIOUS BASED ON THE MERCK '196 APPLICATION⁵¹ AND THE FUJISAWA PATENTS

78. Having seen the substituted diphenyl-heterocycle pharmacophore of the Merck '196 application, a person of ordinary skill in the art would have looked for known compounds that have this pharmacophore because they would be expected to be COX-2 selective. A person of ordinary skill in the art would have wanted to find all known example compounds having this pharmacophore and to use that information to develop new compounds within the pharmacophore.

⁴⁸ See P. N. Craig, "Guidelines for Drug and Analog Design," Chapter 8 in Burger's Medicinal Chemistry, Fourth Edition, Part I, The Basis of Medicinal Chemistry (ed. M. E. Wolff 1980); W. O. Foye, Principles in Medicinal Chemistry (1974).

⁴⁹ Searle/Monsanto internal data confirms that log P is relatively high for diphenyl-heterocycle compounds and would likely need to be reduced. See PFC 00655886-907.

⁵⁰ See P. Prasit, above, at 67.

⁵¹ I have been told that the disclosure of the Merck '196 application is prior art under United States law.

79. A person of ordinary skill in the art would have found the largest number of examples of this pharmacophore in published European Patent Application No. 0 418 845 (“the EP ‘845 patent”) and published European Patent Application No. 0 554 829⁵² (“the EP ‘829 application”), which are Fujisawa Pharmaceutical Company patent applications (collectively, “the Fujisawa references”).

80. The Fujisawa references teach many anti-inflammatory pyrazole example compounds that are within the substituted diphenyl-heterocycle pharmacophore of the Merck ‘196 application. The Fujisawa compounds within the substituted diphenyl heterocycle pharmacophore all are pyrazoles with methylsulfonyl as substituent R.

81. The Merck ‘196 application does not expressly disclose any compounds containing pyrazole. However, based on the heterocycles disclosed in the Merck ‘196 application and the teachings of Fujisawa, a person of ordinary skill in the art would have reasonably expected that pyrazole would be suitable in the pharmacophore. Certainly, the Merck ‘196 application does not teach away from using pyrazole as the heterocycle.

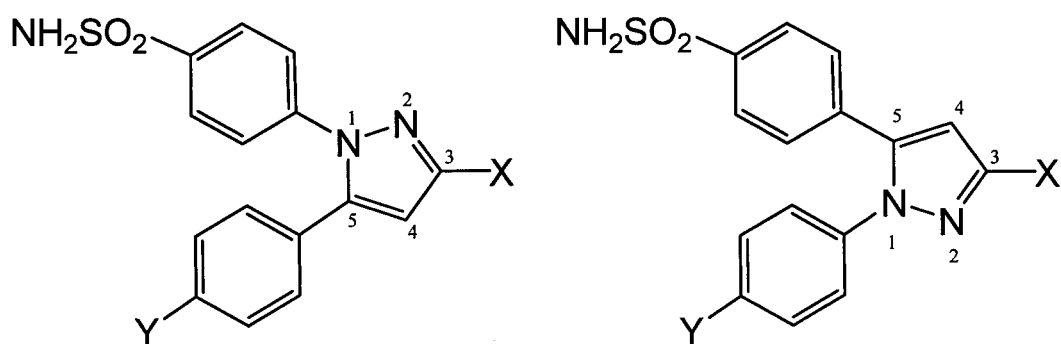
82. The Merck ‘196 application also teaches the interchangeability of a sulfamyl substituent on a phenyl and a methylsulfonyl substituent on a phenyl for obtaining COX-2 selectivity in a substituted diphenyl-heterocycle. In other words, either of these substituents can be used to make a compound of the pharmacophore of the Merck ‘196 application, although the properties can be varied by the selection of one or the other.

83. It would have been obvious for a person of ordinary skill in the art as of November 30, 1993 to make compounds encompassed by the pharmacophore of the Merck ‘196 application by combining the pyrazole taught in the Fujisawa references (but not expressly taught in the

⁵² Teva Ex. 40.

Merck '196 application) with the sulfamyl taught in the Merck '196 application (but not in the Fujisawa references).

84. The result would have been one of the substituted diphenyl-pyrazole compounds shown in the figure below:



85. To complete the compounds, a person of ordinary skill in the art would simply need to select optional substituents "X" and "Y" in the figure above from among those well known to medicinal chemists.

86. As to substituent "X," a person of ordinary skill in the art would have been motivated to use a trifluoromethyl (CF₃) or cyano (CN) substituent based on the *in vitro* biological data given in the Fujisawa references. These data refer to example compounds that are encompassed by the pharmacophore of the Merck '196 application.

87. As to substituent "Y," the Merck '196 application and the EP '845 application show a preference for fluoro (F), while the EP '845 application also shows a pattern of using methoxy (OCH₃), methyl (CH₃), and nitro (NO₂) substituents in addition to fluoro.⁵³ A person of ordinary skill in the art would have known that a nitro substituent is not often used in commercial drugs and would have eliminated this option.

⁵³ The EP '829 application shows a pattern of using more complicated substituents as substituent "Y". Therefore, in the first instance, a person of skill in the art would follow the teachings of the Merck '196 application and the EP '845 application.

88. A person of ordinary skill in the art would also have been motivated to make a compound having a reasonably short pharmacokinetic half-life. A compound having too long a pharmacokinetic half-life would remain stored in the body for too a long time, thereby increasing the risk of side effects.

89. A person of ordinary skill in the art would have known that a substituted diphenylpyrazole compound having a CF₃ substituent on the heterocycle and a halogen substituent on the 4-position of one of the phenyl groups might have a long half life after absorption because these halogen-containing substituents tend to block metabolism.⁵⁴ This is especially true because the SO₂-containing substituent on phenyl "A" also metabolizes slowly.⁵⁵

90. To obtain a compound with a shorter half-life, a person of ordinary skill in the art would have been motivated to replace the fluorine at substituent "Y" with a methyl or methoxy substituent. The methyl or methoxy substituent would provide a "metabolic handle," which is a substituent that is metabolized in a relatively short time to provide faster clearance and shorter half-life than a halogen substituent like fluorine or chlorine.⁵⁶ As an example, the compound flumizole demonstrated a short half-life using methoxy substituents on the phenyl groups.⁵⁷

91. Based on the reasoning above, a person of ordinary skill in the art would have arrived at a series of compounds shown in the figure above where "X" is trifluoromethyl or cyano and "Y" is fluoro, methoxy, or methyl. These options would result in twelve obvious compounds, one of which is celecoxib.

⁵⁴ A. Korolkovas, *Essentials of Molecular Pharmacology* (1970), p. 47, p. 72.

⁵⁵ See Mikes F; Boshart G; Ganz A J; Waser P G, "3-Chloro-4-(phenylsuccinimido)-benzenesulfonamide (GS 385), a new anticonvulsant: its quantitative determination, pharmacokinetics and metabolism using high performance liquid chromatography," 29(10) *Arzneimittel-Forschung* 1583-8 (1979); Asano, T.; Inoue, T.; Kurono, M., "Disposition of azosemide. I. Distribution, metabolism and excretion following intravenous administration to rats," 104(11) *Yakugaku Zasshi* 1181-90 (1984).

⁵⁶ A. Korolkovas, *Essentials of Molecular Pharmacology* (1970).

⁵⁷ See E. H. Wiseman, H. M. McIlhenny, J. W. Bettis, "Flumizole, a New Nonsteroidal Anti-Inflammatory Agent," 64 *J. Pharmaceutical Sci.* 1469-75 (1975).

92. In conclusion, it would have been obvious as of November 30, 1993 to make celecoxib and similar compounds based on the pharmacophore of the Merck '196 application and the teaching of a pyrazole and various common organic chemical substituents in the Fujisawa references.

X. THE PHARMACOPHORE OF THE MERCK '196 APPLICATION IS A BETTER STARTING POINT THAN A "LEAD" COMPOUND

93. Lead compounds can be used as conceptual starting points for the design and synthesis of a series of analog compounds that can be tested for activity against a target enzyme. Lead compounds can also be used as a standard for activity testing in the laboratory.

94. As set forth above, the Merck '196 application teaches a pharmacophore that can be used to prepare compounds reasonably expected to be COX-2 selective. In view of this teaching, one would not need a conceptual "lead" compound from the Merck '196 application to use as a starting point for the design of new COX-2 selective compounds – instead choosing to use the pharmacophore as a "lead" for this purpose.

95. I have been asked which compounds of the Merck '196 application a person of skill in the art would choose as leads. As set forth above, I would choose the pharmacophore as a lead. However, if I had to choose specific lead compounds, I would make that choice from the compounds of Examples 1-14 of the Merck '196 application, compounds stated to have COX-2 selectivity of over 100, and compounds for which COX-1 and COX-2 inhibition data is provided.

96. In my opinion, a person of skill in the art would choose the compounds of Examples 2, 8, 11, and 13 as leads, because those compounds are all within the pharmacophore of the Merck '196 application, and based on their heterocycle substitutions, provide maximum flexibility for the design of additional compounds commensurate with the pharmacophore of the Merck '196 application.

97. Having made such a choice, I would use these compounds and the pharmacophore taught in the '196 application to look for known compounds that have the same pharmacophore that could provide a basis for modifying the lead compounds (but not the pharmacophore) to obtain new compounds within the pharmacophore and therefore reasonably expected to be COX-2 selective.

98. I would then use the compounds within the pharmacophore that I found and proceed as set forth above, with the same result – 12 obvious compounds, one of which is celecoxib.

XI. THE INVENTORS DID NOT DISCLOSE THEIR PREFERRED CRITERIA AND DATA – BOTH OF WHICH ARE NEEDED FOR OPTIMAL USE OF THE ALLEGED “INVENTION” OF THE ASSERTED CLAIMS OF THE PATENTS IN SUIT

99. I have reviewed the depositions transcripts of Mr. Joseph Bullock, Dr. John Talley and many of the other inventors. I have also reviewed documents produced by Searle. I rely on those materials to support my testimony below.

A. Searle's COX-2 Inhibitor Project

100. It is my understanding that the compounds covered by the asserted claims of the patents in suit were the product of Searle's COX-2 Inhibitor Program.

101. The hypothesis underlying this program was that compounds that inhibited COX-2 without inhibiting COX-1 would not cause the high incidence of gastrointestinal side effects associated with most common NSAIDs. Thus, the goal of the Cox-II Inhibitor Program was to find anti-inflammatory compounds suitable for commercialization that inhibited COX-2 without substantially inhibiting COX-1.⁵⁸

⁵⁸ See Talley Tr. at 258:8-259:10; Bullock Tr. at 160:21-161:6; Carter Tr. 15-17; Graneto Tr. 22:6-24; 25:20-26:1.

102. The patents in suit each identify the intended use of the claimed compounds: “[t]he *compounds* [of the invention] are useful as anti-inflammatory agents, such as for the treatment of arthritis, *with the additional benefit of having significantly less harmful side effects*.”⁵⁹

B. Searle’s Cox-2 Inhibitor Program Criteria

103. By November 30, 1993, the inventors of the patents in suit had a set of criteria to assess the preferred compounds in the Cox-2 Inhibitor Program. Those criteria included, in order, the following:

- (a) Potent inhibition of Cox-2 with Cox-2 selectivity greater than 100;
- (b) Oral activity in the rat carrageenan paw edema assay, rat adjuvant arthritis assay, and analgesia assay
- (c) No toxicity in the stomach or intestine; and
- (d) Desirable duration of action.⁶⁰

104. The same criteria are identified in the minutes of a December 6, 1993 Product Lead Team meeting attended by two of the inventors, Dr. Talley and Dr. Collins.⁶¹

105. The inventors also had a product testing scheme that they followed, which also included, in the following order, testing for COX-2 selectivity, *in vivo* activity (carrageenan paw edema and pain, adjuvant arthritis, GI lesions) and high dose pharmacology.⁶²

C. The First Criteria – COX-2 Selectivity

106. The first criteria was COX-2 selectivity. The inventor’s testified about their preferences for COX-2 selective compounds, because such compounds were expected to have significantly less harmful side effects.⁶³

⁵⁹ See the ‘823 patent, 3:23-25; the ‘165 patent, 3:24-27; and the ‘068 patent, 4:54-56.

⁶⁰ Teva Exhibit 29 at PFC 319372; *see also* Carter Tr. 22-24; Graneto Tr. 30-31; 42:9-16; 46:2-14; 48:19-24; Penning Tr. at 87-100.

⁶¹ Teva Exhibit 152 at PFC 650178.

⁶² Teva Exhibit 29 at PFC 319374; Penning Tr. at 100-103.

107. The inventor's further testified that they could not tell whether a compound was COX-2 selective without having relative potency and selectivity data.⁶⁴

1. The Inventors Had Cox-2 Selectivity Data

108. In addition to having preferred criteria, including COX-2 selectivity, before November 30, 1993, the inventors had COX-2 selectivity data for most of the examples of the '823 and '165 patent.⁶⁵ I also understand that as of November 30, 1993 there existed selectivity data for many other compounds within the scope of the asserted claims of the '823 and '165 patents.⁶⁶

109. My understanding is that the inventors used this data to help determine which compounds were the best, and to determine which compounds to pursue further in their Cox-II Inhibitor Project.

110. In the '823 and '165 patents, I see nothing that indicates the inventors' preferences for COX-2 selective compounds. I also do not see any COX-2 selectivity data in those patents.

⁶³ Khanna Tr. 270-272; 280:17-24; Penning Tr. 90:3-14; Carter Tr. 18-24; Graneto Tr. 39:17-22, 44:2-8, 50:8-51:5; Talley Tr. at 72-74; 261:20-262:15; Miyashiro Tr. 72:2-7.

⁶⁴ Khanna Tr. 273:21-274:22; Graneto Tr. 202:9-17; 203:5-21. I note that many of the inventors testified that they expected all of the compounds of claim 1 of the '823 patent application, as filed, to be COX-2 selective. *See, e.g.,* Penning Tr., 190:20-191:4.

⁶⁵ Plaintiffs have admitted that at least one of the inventors of the patents in suit knew of such data for Examples 1, 1a-1j, 2-4, 9-12, 14-15, 17-20, 22-27, and 29 before November 30, 1993. *See* Pfizer's Responses to Defendant Teva Pharmaceutical USA, Inc.'s Third Set of Requests for Admission Nos. 174-187, 192-195, 197-198, 200-203, and 205-211. As to selectivity data on other examples, see: PFC 1554656 and 1554690 (Example 5), PFC 1555162 and 1555190 (Example 6), PFC 1554541 and 1554559 (Example 7), PFC 1554541, 1554559, and 1555132 (Example 8), PFC 1555132, 1555146, and 1554656 (Example 13), PFC 1554631 (Example 16), and PFC 1554613 and 1554608 (Example 21).

⁶⁶ *See* PFC 1554631 (SC 58692); PFC 1555132 (SC 58729, SC 58759); PFC 1555109 (SC 58887, SC 58940, SC 58943); PFC 1555218 (SC 58944); PFC 1555190 (SC 58946, SC 58952); PFC 1555218 (SC 58947); PFC 1555246 (SC 58971, SC 58981, SC 59041, SC 59042, SC 59060, SC 59061, SC 59066); PFC 1555278 (SC 58903); PFC 1555294 (SC 59045, SC 59046, SC 59047); PFC 1204063 (SC 59159); and PFC 1555314 (SC 59133).

2. A Person Of Ordinary Skill In The Art Would Have Needed To Know About The COX-2 Selectivity Preference And Data To Best Practice The Alleged "Invention" Of The Asserted Claims

111. A person of ordinary skill in the art would need to know about such preferences, so that the person of ordinary skill in the art would have a means to assess which of the millions of compounds covered by asserted claim 1 of the '823 patent were the best for their intended use as anti-inflammatory agents, such as for the treatment of arthritis, with the additional benefit of having significantly less harmful side effects.

112. Without knowing the inventors' preference for COX-2 selective compounds, a person of ordinary skill in the art would at least need to see the admittedly existing *in vitro* data that the inventors had, because this data could have been used, in conjunction with the COX-2 hypothesis, to give direction as to which of the millions of compounds covered by the genus of asserted claim 1 of the '823 patent are the most selective, and therefore, the best for their intended use as anti-inflammatory agents, such as for the treatment of arthritis, with the additional benefit of having significantly less harmful side effects.

113. For the same reasons, a person of skill in the art would need to know the inventors' preferences or have the existing selectivity data to determine the best compounds to use from asserted claims 2, 3, 7, 8, 11 and 13 of the '823 patent, and claims 1-5, 15, 16 and 18 of the '165 patent.

114. In contrast to the lack of disclosure of COX-1 and COX-2 information in the '823 and '165 patents, the Merck '196 patent discloses such information. For example, the Merck '196 application is entitled: "Phenyl Heterocycles As Cox-2 Inhibitors."⁶⁷

115. The Merck '196 application further states:

⁶⁷ '196 application, at page 1.

By virtue of its high cyclooxygenase-2 (COX-2) activity and/or selectivity for cyclooxygenase-2 over cyclooxygenase-1 (COX-1) as defined above, compounds of formula I will prove useful as an alternative to conventional nonsteroidal anti-inflammatory drugs (NSAID's) particularly where such nonsteroidal anti-inflammatory drugs may be contra-indicated such as in patients with peptic ulcers, gastritis, regional enteritis, ulcerative colitis⁶⁸

116. The Merck '196 application also states:

[W]e have found that the Compounds of the examples are more than 100 times more effective in inhibiting Cox-2 than they are at inhibiting Cox-1. In addition they all have a Cox-2 IC₅₀ of 1 nM to 1 uM. By way of comparison, Ibuprofen has an IC₅₀ for Cox-2 of 1 uM, and Indomethacin has an IC₅₀ for Cox-2 of approximately 100 nM.⁶⁹

D. Example 30 Exemplifies The Need For Disclosing Inventor Preferences

117. The '823 and '165 patents state: "A *specific compound of particular interest* within Formula I is 4-[1-(4-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazole-5-yl]benzenesulfonamide, or a pharmaceutically acceptable salt thereof."⁷⁰ This is the only single compound that the specifications identify as "of particular interest." The referenced compound is Example 30 of the '823 and '165 patents (which is also example 262 of U.S. Patent No. 5,760,068⁷¹ ("the '068 patent")).

118. Dr. Talley, the first named inventor, testified that when he signed the application for the '823 patent, he understood the term "particular interest" to refer to a compound that had "the best anti-inflammatory characteristics."⁷²

119. However, as of the November 30, 1993 filing of the application for the '823 patent, Plaintiffs had not tested the compound of Example 30, SC-59156, for COX-2 selectivity.⁷³

⁶⁸ '196 application, at page 10, lines 22-28.

⁶⁹ '196 application, at page 12, lines 2-7.

⁷⁰ See '823 Patent, 12: 30-33; '165 Patent 12:31-34 (emphasis added).

⁷¹ See Teva Ex. 8.

⁷² See Talley Tr. 54:12-18.

Indeed, testing of SC-59156 indicated that it was a potent COX-1 inhibitor,⁷⁴ a characteristic the inventors wanted to avoid.⁷⁵

120. A person of ordinary skill in the art would be very interested in Example 30, the only compound that the specification identifies as “of particular interest”. Without knowing that the inventors preferred COX-2 selectivity and wanted to avoid potent COX-1 inhibition, the person of ordinary skill in the art would have no way of knowing that despite being identified as a compound “of particular interest”, Example 30 in reality does not meet the inventors’ criteria for preferred compounds.

E. The Additional Criteria: Rat Carrageenan Paw Edema, Rat Adjuvant Arthritis, Analgesia , And Ulcerogenicity

121. As set forth above, each of the patents in suit indicates that the compounds covered by the claims “are useful as anti-inflammatory agents, such as for the *treatment of arthritis, with the additional benefit of having significantly less harmful side effects.*”

1. The Adjuvant Arthritis Assay And Ulcerogenicity Assay Are Important When Developing Drugs For Chronic Arthritis Use

122. A person of skill in the art would understand that the treatment of arthritis usually requires chronic care – *i.e.*, administration of medications over long periods of time. A person of ordinary skill in the art would also know that such treatment, with common NSAIDs, could lead to life threatening ulcers.

123. The adjuvant arthritis assay is considered a “chronic model” that provides information on the efficacy of a compound for longer-term use to treat pain and inflammation

⁷³ Koboldt Tr. 229:13-18

⁷⁴ See Koboldt Tr. 230:10-231:13.

⁷⁵ See Docter Tr. 79:16-20; Carter Tr. 23:21-24:1; Graneto Tr. 148:9-18.

associated with chronic arthritis in humans. Therefore, it is an important assay in relation to drugs for use in treating the chronic symptoms of arthritis.

124. Furthermore, short of clinical testing, the best assay for determining whether a compound will cause ulcers in humans is an ulcerogenicity assay, which tests for the level of a compound necessary to cause ulcers in the test subject.

2. The Inventors Had Preferences For The Activity Of Compounds In The Adjuvant Arthritis And Ulcerogenicity Assays

125. As set forth above, the COX-2 Inhibitor Project Criteria and the COX-2 Inhibitor Project Testing Scheme each included preferred activity in the adjuvant arthritis and ulcerogenicity assays.⁷⁶ The inventors knew about these criteria.⁷⁷

126. According to Dr. Carter, one of the inventors, the “prevailing understanding” was that performance in the rat adjuvant arthritis test was more predictive of human dosing than the rat paw edema test.⁷⁸ Dr. Collins testified that the adjuvant arthritis assay “is a key assay for a clinical indication for arthritis.”⁷⁹

3. The Patents In Suit Do Not Provide Any Adjuvant Arthritis Or Ulcerogenicity Data

127. As set forth above, the inventors considered the adjuvant arthritis assay to be key assay for a clinical indication for arthritis. As to ulcerogenicity data, short of clinical trials, it is the best data to assess the ulcerogenicity of a compound.

⁷⁶ See Teva Ex. 29 at PFC 319374; Teva Ex. 152 at PFC 650178; Penning Tr. at 87-103.

⁷⁷ See Talley Tr. at 72-74, 117:20-118:10; Khanna Tr. 221:23-223:22.

⁷⁸ See Carter Tr. 193:20-25.

⁷⁹ See Collins Tr., 51:9-17; Teva Ex. 150 at PFC 1578328.

128. As of the November 30, 1993 filing date of the '823 patent (the first application filed for the patents in suit), Plaintiffs had obtained adjuvant arthritis data on the compounds of examples 1, 1c, 1f, 1g, and 2⁸⁰, and ulcerogenicity data on at least the compound of example 1.⁸¹

129. None of the inventors' preferences regarding activity in the adjuvant arthritis assay or ulcerogenicity assay is in the patents in suit. Furthermore, none of the above identified adjuvant arthritis ulcerogenicity assay data is in the patents in suit. Instead, the '823 and '165 patents have rat paw edema data and analgesia data, neither of which tell you whether the compounds will be effective for chronic use in the treatment of arthritis, or whether the compound will cause ulcers.

130. The '068 patent adds COX-1 and COX-2 IC₅₀ data. As to ulcerogenicity, the hypothesis at the time was that COX-2 selective compounds would be anti-inflammatory with significantly less harmful side effects. Although one might reasonably expect a COX-2 selective compound to be non-ulcerogenic, the more accurate test is a test of ulcerogenicity.

131. In my opinion, to know which of the many compounds of the asserted compound, composition and method of use claims would be the best to use for their intended purpose – “the treatment of arthritis, with the additional benefit of having significantly less harmful side effects”, one of skill in the art would have needed to know the inventors' preferences with regard to activity in the adjuvant arthritis and ulcerogenicity tests.

F. THE OBVIOUSNESS OF CELECOXIB IS CONFIRMED BY OBJECTIVE REAL WORLD EVIDENCE

132. I have reviewed various sources of real world evidence that confirm the obviousness of celecoxib. For example, the pharmacophore taught by the Merck '196

⁸⁰ See Teva Ex. 52 at PFC 1220722-23.

⁸¹ See Teva Ex. 52 at PFC 1220722-23; PFC 650448.

application is consistent with the pharmacophores developed by both Searle and Merck in their respective COX-2 inhibitor programs, pharmacophores that could be used to design compounds reasonably expected to be COX-2 selective.⁸²

133. The objective real world evidence also shows that Searle was concerned about the obviousness of its pyrazole compounds in view of the Fujisawa references,⁸³ and that external reviewers were concerned about the obviousness of Searle's pyrazole compounds in view of DuP 697.⁸⁴

134. In their COX-2 inhibitor program, Searle considered the discovery that sulfamyl could be used to make COX-2 selective compounds to be an important discovery.⁸⁵ But as described above, Merck's '196 application shows that Merck made the same discovery.

135. Finally, three of the 12 obvious compounds identified above fall within the claims of the '823 patent, and I understand that those compounds are COX-2 selective.

⁸² See Teva Ex. 241 at PFC 633927 and Teva Ex. 244; See P. Prasit, D. Riendeau, and C. C. Chan, "Discovery of Vioxx (rofecoxib)," Ch. 3 in "Therapeutic Roles Of Selective COX-2 Inhibitors," ed. by JR Vane (2001), at pp. 66-67.

⁸³ See Teva Exhibit 68 at PFC 322022; Penning Tr. 150:14-22. In fact, during prosecution of the '196 application, Merck disclosed the Fujisawa '845 application to the Patent Office, showing that Merck also thought it was material to prosecution of their application for diaryl heterocyclic compounds.

⁸⁴ See Teva Ex. 146 at PFC 0677714.

⁸⁵ See Teva Ex. 150 at PFC 1578329-30; Collins Tr. 50:11-18, describing Teva Ex-150; Teva Ex. 3 at PFC 1218943. See also Teva Ex. 234A, a Forbes article describing the development of Celecoxib, and portions of Dr. Talley's testimony regarding that article: Talley Tr. 38:12-24, 42:1-11.

XII. SUPPLEMENTATION AND REBUTTAL

136. I hereby reserve my right to supplement this report and/or to rebut any expert opinion or testimony offered in response to the opinions stated herein. I further reserve the right to rely on demonstratives to support any testimony offered on behalf of Teva.

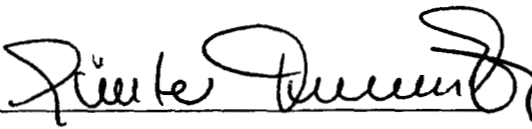
Dated: May 5, 2006 
Guenter Trummelitz, Ph.D.

EXHIBIT A

GUENTER TRUMMLITZ, PhD
Consultant
Buchenweg 27
D-88447 Warthausen
Germany

Curriculum Vitae

Personal Information

| | |
|-------------------------|---|
| Date and place of birth | 24 January 1944 in Radebeul/Dresden, Germany |
| Marital status | Married, 2 children |
| Education | 27 February 1964: Final high school examination: Goethe-Gymnasium, Frankfurt/Main 13 February 1969: Diploma in chemistry at University Darmstadt, Germany 3 May 1971: Ph.D. (Dr. rer. nat.) at University Darmstadt, Germany |

Career History

| | |
|-------------|---|
| 1971 – 1973 | Research fellow at the Institute of Molecular Biology of Syntex Research (now Roche Bioscience) in Palo Alto, California, USA |
| 1973 – 1993 | Several appointments at Dr. Karl Thomae GmbH (now Boehringer Ingelheim Pharma KG), Biberach/Riss: 1973 – 1986: Head of pharmasynthesis laboratory 1979 – 1986: Computer assisted drug design 1986 – 1988: Head of development coordination department 1988 – 1993: Project leader |
| 1994 – 2003 | International project leader at Boehringer Ingelheim Head Office (BI GmbH) in Ingelheim/Rhein |
| Since 2003 | Consultant and scientific advisor; since 2005 freelance work |

Business Experience

Pharmaceutical research and drug design:

- Synthesis of drug development compounds in 6 indication areas
- Implementation of computational chemistry
- Development of research strategies
- Inventor and co-inventor of 2 launched NCEs, meloxicam (Mobic®) and nevirapine (Viramune®), respectively.

Pharmaceutical development:

- Predevelopment and preclinical development project management
- Implementation of project management for international drug development, international registration, worldwide launch and marketing,

- Lecturer for project management at the FORUM-Institute for Management
- Cooperations with CROs and co-development partners
- Responsible project leader for development, registration and launch of meloxicam (Mobic®)
- Project management for the first international development and launch at Boehringer Ingelheim

Development Strategies:

- Involvement in portfolio analyses and drug candidate selection
- Establishing new organizational processes for drug development
- Lecturer at the International Conferences on MANAGING PROJECTS
In worldwide drug development (GPM)

Consultant and Advisor:

- Development consulting for Nitric Oxide-containing COX-inhibitors
- Scientific Advisor for Medicinal Chemistry
- Scientific advisor for COX-2 inhibitors and Nonsteroidal Anti-inflammatory Agents
- Scientific advisor for new indications of COX-2 inhibitors

Publications and Patents

52 scientific publications:

medicinal chemistry,
pharmacology and
drug development

52 scientific lectures:

medicinal chemistry,
pharmacology of COX-2 inhibitors,
drug research and development

80 patent applications, incl 45 issued:

new substances for pharmaceutical use,
pharmaceutical products and processes

Lecturer and Member of Scientific Societies

Lecturer: FORUM Institute for Management GmbH
Medicinal Chemistry Sections of several Scientific Societies
German Gesellschaft Deutscher Chemiker

Present Address

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Warthausen, March 20, 2006

GUENTER TRUMMLITZ, PhD
Consultant
Buchenweg 27
D-88447 Warthausen
Germany

List of Lectures and Poster Presentations

1. Fischer W, Lichtenthaler FW, Mayer N, Trummlitz G, Voss P, Zinke H
Ein neuer Zugang zu Inosatriaminen, Triaminozuckern und Triamino-Nucleosiden
Lecture at the Bürgenstock-Conference on Stereochemistry, Luzern, Schweiz, 8 May 1969.
2. Trummlitz G
Bestimmung der konformativen und elektronischen Eigenschaften von Pharmaka-Molekülen: Hilfsmittel im Drug-Design
Lecture at the Freie Universität Berlin, 3 May 1984.
3. Trummlitz G, Luger P
Conformational Analysis of the Antiulcer Drug Pirenzepine
Posterpresentation at the 25th Annual Medicinal Chemistry Symposium: Recent Advances in Techniques for Drug Design and Conformational Analysis, Buffalo, USA, 11 Jun 1984.
4. Bietti G, Micheletti R, Pagani F, Giachetti A, Donetti A, Trummlitz G
(Guanidionothiazol) phenylformamidines as H₂-Receptor Antagonists
Posterpresentation at the VIIIth Int. Symp. on Medicinal Chemistry, Uppsala, Schweden, 29 Aug 1984.
5. Trummlitz G, Eberlein W, Engel W, Schmidt G
Conformational Analysis of Antiulcer Agents Structurally Related to Pirenzepine
Lecture at the VIIIth Int. Symp. Medicinal Chemistry, Uppsala, Sweden, 31 Aug 1984.
6. Trummlitz G, Eberlein W, Engel W, Trummlitz G
Molekulare Konformationsanalysen an m₁-selektiven Antimuskarinika vom Pirenzepin-Typ
Lecture at the Jahrestagung der Gesellschaft Deutscher Chemiker, Fachgruppe Medizinische Chemie, Freiburg, 6 Sep 1984.
7. Luger P, Trummlitz G
Konformationsanalyse des Ulcusterapeutikums Pirenzepin durch Röntgenstrukturanalyse, empirische und semiempirische Rechnungen

Lecture at Heidelberger Symposium „Struktur-Wirkungs-Beziehungen bei Biomolekülen“, Heidelberg, 8 – 12 Oct 1984.

8. Eberlein W, Trummlitz G, Engel W, Schiavi G
New Analogues of Pirenzepine: Structure-Activity-Relationships of M₁-selective Antimuscarinics
Posterpresentation auf dem Second International Symposium: Subtypes of Muscarinic Receptors, Boston, 22 – 24 Aug 1985
9. Trummlitz G
Conformational Analyses of Drug Molecules Using Molecular Mechanics Calculations
Lecture at the Symposium "Molecular Geometry and Drug Action" of the European Crystallographic Meeting, Turin, 2 – 6 Sep 1985.
10. Trummlitz G
An Approach for the Calculation of Amine out-of-plane Angles in Drug Molecules Using a Modified Version of MMPI
Posterpresentation at the 1st Gordon Research Conference on Computational Chemistry, New London, N. H., USA, 20 Aug 1986.
11. Trummlitz G, Wagner H-U
Molecular Electrostatic Potentials Including Polarization Corrections of Some Adrenergic Receptor Agonists
Posterpresentation at the IX. Int. Symp. Medicinal Chemistry, Berlin, 14 – 18 Sep 1986.
12. Trummlitz G, Eberlein W, Engel W, Mihm G, Luger P, Giachetti A
Stereochemical Aspects of the Interaction of m₁-selective Pirenzepine-Analogs with the Muscarinic Receptor
Lecture at the IX. Int. Symp. Medicinal Chemistry, Berlin, 14 – 18 Sep 1986.
13. Rudert R, Buschmann J, Luger P, Gregson D, Trummlitz G
Strukturelle Aspekte von Süß- und Bitterstoffen
Posterpresentation at the Deutschen Fachtagung für Kristallographie, Berlin, 1986.
14. Trummlitz G, Engelhardt G
Meloxicam: Structural Aspects of a New NSAID with Improved Therapeutic Properties
Posterpresentation at EULAR, XI. European Congr. of Rheumatology Athens, Greece, 28 Jun – 4 Jul 1987.
15. Rudert R, Buschmann J, Luger P, Gregson D, Trummlitz G
Structure/Taste Relationships of Artificial Sweeteners
Posterpresentation at the XIV. International Congress of the International Union of Crystallography, Perth (Australia), 12 – 20 Aug 1987.
16. Engel W, Trummlitz G, Eberlein W, Mihm G, Mayer N, Hasselbach K
Stereochemical Aspects of Tricyclic Antimuscarinics Structurally Related to the m₂-Antagonist AF-DX 116 - Implications with Respect to Receptor Selectivity

Lecture at the Jahrestagung der Gesellschaft Deutscher Chemiker, Fachgruppe Medizinische Chemie, Freiburg, 1987.

17. Buschmann J, Rudert R, Luger P, Trummlitz G
Electron Deformation Density of Saccharin Derivatives
Lecture at the Sagamore IX. Conference on Charge, Spin and Momentum Densities, Luso-Bucaco (Portugal), 26 Jun – 2 Jul 1988.
18. Engel W, Eberlein W, Mihm G, Trummlitz G, Mayer N, Doods H, Hasselbach K
Tricyclic Pirenzepine-like Compounds - Tools Suitable for Subclassification of Muscarinic Receptors
Posterpresentation at the Gordon Research Conference on Medicinal Chemistry New London, N. H., USA, 1988.
19. Engel W, Eberlein W, Mihm G, Trummlitz G, Mayer N, Hasselbach K
Tricyclic Pirenzepine-like Compounds - Tools Suitable for Subclassification of Muscarinic Receptors
Lecture at the 10. International Symposium on Medicinal Chemistry, Budapest, Aug 1988.
20. Engelhardt G, Trummlitz G
Biological Activity of the Main Metabolites of Meloxicam
Lecture at the 3rd Interscience World Conference on Inflammation, Monte Carlo, 15 - 18 Mar 1989.
21. Trummlitz G, Wink, P
Erfolgreiches Pharma-Projektmanagement - Steuerung und Optimierung der Produktentwicklung
1-Day Seminars at the FORUM-Institut für Management, Frankfurt/Main, 20 Jun 1988. Updated on: 05.10.88, 17.01.89, 01.06.89, 24.09.89, 12.03.90, 24.06.90, 01.10.90, 10.12.90, 07.03.91, 24.06.91, 20.01.92
22. Trummlitz G, Wink P
Effectiveness and Efficacy in Research and Development of New Drugs in Pharmaceutical Industry
1-Day-Seminar, Milano, 28 Jan 1991
23. Trummlitz G
Team Building: Effiziente Arzneimittelentwicklung durch Integration von F & E, Klinik und Marketing unter multinationaler Beteiligung
Lecture at the GPM-Tagung „Projektmanagement für Pharma-F & E- Projekte“, Würzburg, 5 - 6 Jun 1991.
24. Trummlitz G
Internationale Projektarbeit im Entwicklungsbereich der Pharmaindustrie
Lecture at the Symposium „Projektmanagement in der Forschung und Entwicklung“ Vienna, 25 Sep 1992.
25. Trummlitz G

Team Building and Project Work: Changes for the Better?

Lecture at the GPM : Internationale Conference on "Managing Projects in Worldwide Drug Development", Garmisch-Partenkirchen, Germany, 5 - 8 Sep 1993.

26. Daneck K, Engel W, Trummlitz G
Importance of physico-chemical properties in the activity profile of meloxicam.
Posterpresentation at Meeting "New insights into Anti-Inflammatory Therapy and its benefits", Cannes, France, 14 - 16 Oct 1994.
27. Fiebich BL, Lieb K, Ganter U, Pairet M, Trummlitz G, Engelhardt G, Berger B, Bauer J
Cyclooxygenase-2 expression in human monocytes
Posterpresentation at the William Harvey Research Conference "Improved Non-Steroid Anti-Inflammatory Drugs: COX-2 Enzymes Inhibitor", London, 10 - 11 October 1995.
28. Herbette L; Vecchiarelli M; Trummlitz G
NSAID mechanism of action: the role of intracellular pharmacokinetics.
Lecture at the William Harvey Research Conference "Improved Non-Steroid Anti-Inflammatory Drugs: COX-2 Enzyme Inhibitors", London, 10 - 11 Oct 1995
29. Busch U, Tuerck D, Lehmann H, Trummlitz G
The importance of unbound plasma concentrations of meloxicam for prediction of safety in various animal species in comparison to man.
Posterpresentation at EULAR, 13 Eur Cong of Rheumatology, Amsterdam 18 – 23 Jun 1995
30. Daneck K, Engel W, Trummlitz G
Importance of physico-chemical properties in the activity profile of meloxicam.
*25th Scandinavian Congress of Rheumatology, Lillehammer, Jun 1994,
9th Int Conf on Prostaglandins and Related Compounds, Florence, Jun 1994,
20th Symp of the European Society of Osteoarthritis, Bari, Sep/Oct 1994,
2nd Int Cong of the Osteoarthritis Research Society, Orlando, Dec 1994*
31. Fiebich BL, Lieb K, Pairet M, Trummlitz G, Engelhardt G, Berger M, Bauer M, Gebicke-Härter P, Bauer J
Expression and regulation of inducible COX-2 in rat microglia and its inhibition by NSAIDs
WHR Conference: New targets in inflammation: inhibitors of COX-2 or adhesion molecules, New Orleans, USA, 15 - 16 April 1996 (1996)
32. Trummlitz G
Mode of Action of NSAIDs – COX-2 Selectivity of Meloxicam
Lecture at the European Opinion Leader Meeting, Vienna, 1 – 2 Dec 1996
33. Trummlitz G, Wink, P
Time to BREAK EVEN
Seminar of the FORUM-Institute for Management, Heidelberg, 11 Feb 1999 and

Frankfurt/Main, 20 Jan 2000

34. Trummlitz G
Inhibidores COX-2: Mitos y Realidades
Chairmanship of the Iberoamerican Opinion Leaders Conference, Cancun Mexico, 11 – 13 Jun 2000
35. Trummlitz G
Meloxicam (Mobic™): Pharmacological and Clinical Profile
MOB – Scientific Meetings, Tokyo, 17 Mar 2001 and Osaka, 24 Mar 2001
36. Trummlitz G
Pharmacology of Selective COX-2 Inhibitors
Plenary Lecture at the International Symposium, Sun City, South Africa, 23 Apr 2001
37. Trummlitz G
Selective COX-2 Inhibition: Profile of Meloxicam
National Opinion Leader Conference: COX-2 Symposium 2001, Karuizawa, Japan, 12 May 2001
38. Trummlitz G; Wittneben H
Insight into the structural basis of selective cyclooxygenase-2 inhibition.
Posterpresentation at EULAR 2001, Ann Eur Cong of Rheumatology, Prague, 13 - 16 Jun 2001
39. Trummlitz G; Wittneben H
Insight into the structural basis of selective cyclooxygenase-2 inhibition.
Posterpresentation at ILAR 2001, 20th Cong of the International League of Associations for Rheumatology, Edmonton, 26 - 30 Aug 2001
40. Trummlitz G; Wittneben H; Ryn J van
Molecular basis of selective cyclooxygenase-2 inhibition.
Lecture at the 5th World Cong on Inflammation, Edinburgh, 22 - 26 Sep 2001,
41. Trummlitz G; Wittneben H
Insight into the structural basis of selective cyclooxygenase-2 inhibition.
Posterpresentation at the William Harvey Res Conf 'Progress in the Field of Selective COX-2 Inhibitors', Nice, 30 Sep - 2 Oct 2001
42. Ryn J van; Schierok H; Erni I; Schlager S; Trummlitz G; Pairet M
Selective COX-2 inhibition and acid-induced gastric lesions: effect of meloxicam, nimesulide and piroxicam.
Posterpresentation at the William Harvey Res Conf 'Progress in the Field of Selective COX-2 Inhibitors', Nice, 30 Sep - 2 Oct 2001
43. Trummlitz G
Pharmacology of Selective COX-2 Inhibitors: Differences and Similarities
Planary Lecture at the International Opinion Leaders Conference, Nice, France,

3 Oct 2001

44. Trummelitz G, van Ryn J
Molecular Differences in the cyclooxygenase Isoenzymes Responsible for the Selectivity of COX-2 Inhibitors belonging to distinct structural classes
Poster presentation at EULAR 2002, Ann Eur Cong of Rheumatology, Stockholm, 12 - 15 Jun 2002
45. Trummelitz G
INSIGHT INTO THE MOLECULAR BASIS OF SELECTIVE COX-2 INHIBITION
Plenary Lecture at the William Harvey Res Conf 'Evolution of COX Isoenzymes and their Inhibitors', Phuket, 9 - 11 Oct 2002,
46. Trummelitz G
Selective COX-2 Inhibitors: Consequences of Molecular Differences and Similarities
Plenary Lecture at the Symposium "COX-2 Inhibitors: Real Life Conditions", Sorrento, Italy, 14 - 15 Oct 2002
47. Trummelitz, G.
Insight into the molecular basis of selective COX-2 inhibition,
Plenary Lecture at the International Conference on Inflammopharmacology 2003 – VIII Side-Effects of Anti-Inflammatory Drugs Symposium, Sheffield, UK, 22 – 24 April 2003
48. Trummelitz G, Wittneben H, van Ryn J, Harman C, Clayton G, Garavito RM
X-Ray crystallographic analysis and computational docking studies of cyclooxygenase isoform inhibitors.
Poster presentation at EULAR 2003, Ann Eur Cong of Rheumatology, Lisbon, 12 – 15 Jun 2003
49. Trummelitz G, van Ryn J, Klein CT, Clayton G, Powers R, Garavito RM
Structural Analysis of Cyclooxygenase-1 Inhibition and Relevant Interferences with Inactivation by Aspirin
Poster presentation at EULAR 2004, Ann Eur Cong of Rheumatology, Berlin, 9 – 12 Jun 2004
50. Trummelitz G
Design of Selective COX-2 Inhibitors: Biological Basis & Molecular Requirements
Plenary Lecture at the GTCbio Conference Modern Drug Discovery & Development, San Diego, California, 18 - 19 Oct 2004
51. Trummelitz G, van Ryn J, Tr
Structural Analysis of Cyclooxygenase-1 Inhibition and Relevant
Poster presentation at EULAR 2005, Ann Eur Cong of Rheumatology, Vienna, 8 – 11 Jun 2005
52. Trummelitz G

Aspirin and COX inhibitors: does meloxicam affect the anti-platelet effect of aspirin?

Plenary Lecture at the 3rd International Symposium: Pain Management in Rheumatic Conditions: Moving forward, Paphos, Cyprus, 21-22 Oct 2005

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List of Publications

1. Lichtenthaler FW, Trummlitz G, Zinke H
Nucleosides IX. Synthese von Diamino- und Triaminozucker-Nucleosiden
Tetrahedron Lett 16, 1213-1217 (1969)
2. Lichtenthaler FW, Trummlitz G, Emig P
Nucleosides X. Synthesis of Dipeptidyl Aminosugar Nucleosides Structurally Related to Gougerotin
Tetrahedron Lett 24, 2061-2064 (1970)
3. Lichtenthaler FW, Trummlitz G, Bambach G, Rychlik I
Synthese eines biologisch aktiven Gougerotin-Analogons
Angw Chem 83 (9) 331-332 (1971)
Angw Chem Internat Ed Engl 10, 334 (1971)
4. Trummlitz G, Moffatt JG
A Facile Synthesis of the Nucleoside Antibiotic Showdomycin
J Org Chem 38, 1841-1845 (1973)
5. Lichtenthaler FW, Trummlitz G
Structural Basis for Inhibition of Protein Synthesis by Aminoacyl-Aminohexosyl-Cytosine Group of Antibiotics
FEBS Letters 38 (3), 237-242 (1974)
6. Trummlitz G, Repke DB, Moffatt JG
C-Glycosyl Nucleosides VIII. Synthesis of 3-Methylshowdomycin
J Org Chem 40, 3352-3356 (1975)
7. Moffatt JG, Albrecht HP, Jones GH, Repke DB, Trummlitz G, Ohri H, Gupta CM
Advances in the Synthesis of C-Glycosyl Nucleosides
In: Chemistry and Biology of Nucleosides and Nucleotides,
ed. Harmon RE, Robins RK and Townsend LB, Academic Press, New York, 359 (1978)
8. Trummlitz G, Schmidt G, Wagner HU, Luger P
Conformational Analysis of the Antiulcer Drug Pirenzepine-X-Ray Investigations, Molecular Mechanics and Quantum Mechanical Calculations and Comparisons with Structurally or Pharmacologically Related Compounds
Arzneimittelforschung 34 (II), 849-859 (1984)

9. Bietti G, Micheletti R, Pagani F, Giachetti A, Donetti A, Trummlitz G
(Guanidinothiazol) phenylformamidines as H₂-Receptor Antagonists
In: Proceedings of the VIIIth Int. Symp. on Medicinal Chemistry, 2
ed. Dahlbom R, Nilsson JLG, Swedish Pharmaceutical Press, Stockholm, 211 (1985)
10. Trummlitz G, Eberlein W, Engel W, Schmidt G
Conformational Analysis of Antiulcer Agents Structurally Related to Pirenzepine
In: Proceedings of the VIIIth Int. Symp. on Medicinal Chemistry, 2
ed. Dahlbom R Nilsson JGL, Swedish Pharmaceutical Press, Stockholm, 421-423
(1985)
11. Donetti A, Trummlitz G, Bietti G, Cereda E, Bazzano C, Wagner H-U
Conformational Studies of Two Hisamine H₂ Receptor Antagonistic Phenylformamidines: Mifentidine (DA 4577) and its Guanidinothiazole Analogue DA 4643
Arzneimittelforschung, 35 (1a), 306-315 (1985)
12. Luger P, Trummlitz G
Konformationsanalyse des Ulcusterapeutikums Pirenzepin durch Röntgenstrukturanalyse, empirische und semiempirische Rechnungen
Fresenius Z Anal Chem 321, 642-643 (1985)
13. Eberlein W, Trummlitz G, Engel W, Schiavi GB
New Analogues of Pirenzepine: Structure-Activity Relationships of M₁-Selective Antimuscarinics
Subtypes of Muscarinic Receptors 2nd Boston, Aug 22 – 24 1985
Trends Pharmacol Sci 7 (Suppl Feb) 81 (1986)
14. Luger P, Griss G, Hurnaus R, Trummlitz G
The α_2 -Adrenoceptor Agonists B-HT 920, B-HT 922 and B-HT 958, a Comparative X-Ray and Molecular Mechanics Study
Acta Cryst B42, 478-490 (1986)
15. Eberlein W, Trummlitz G, Engel W, Schmidt G, Pelzer H, Mayer N
Tricyclic Compounds as Selective Antimuscarinics 1. Structural Requirements for the Achivement of Selectity Towards the Muscarinic Acetylcholine Receptor in a Series of Pirenzepine and Imipramine Analogs
J Med Chem 30 (8), 1378-1382 (1987)
16. Engel W, Eberlein W, Trummlitz G, Mihm G
Cardioselective Muscarinic Antagonists Pirenzepine and AF-DX 116, two Structurally Related Antimuscarinics with Opposite Receptor Selectivity
Fed Proc 46 (8), 2527-2528 (1987)
17. Trummlitz G, Engelhardt G
Meloxicam: Structural Aspects of a New NSAID with Improved Therapeutic Properties
Clin Exp Rheumatol 5 (Suppl 2), 200, Abstr P146 (1987)

18. Giachetti A, Mittmann U, Brown JH, Goldstein D, Brown Maters S, Birdsall NJM, Hulme EC, Kromer W, Stockton JW, Engel W, Eberlein W, Trummlitz G, Mihm G, Ladinsky H, Giraldo E, Schiavi GB, Mnferini E, Hammer R, Montagna E, Micheletti R, Roeske WR, Bahl J, Vickroy T, Watson M, Yamamura HI, Schuessler R, Boineau J, Watanabe AM
Cardioselective muscarinic antagonists
Fed Proc 46 (8) 2523-2525 Symposium Summary (1987)
19. Rudert R, Buschmann J, Luger P, Gregson D, Trummlitz G
Structure of 4-Hydroxy-1,2-benzisothiazol-3(2H)-one 1,1-Dioxide Sodium Salt (UH-AF 50 NA) at 123 K based on Neutron Diffraction Data
Acta Cryst C 44, 1083-1086 (1988)
20. Eberlein W, Engel W, Trummlitz G, Mihm G, Mayer N, Hasselbach K
Conformational Requirements for M₂-Selectivity Towards the Muscarinic Receptor in a Series of Pirenzepine Analogs
Pharmacol Sci (Suppl): Subtypes of Muscarinic Receptors 3rd Sydney, 29 – 31 Aug 1987
Trends Pharmacol Sci (Suppl) 76, Abstr 2 (1988)
21. Eberlein W, Engel W, Trummlitz G, Schmidt G, Hammer R
Tricyclic Compounds as Selective Antimuscarinics 2. Structure-Activity Relationships of M₁-Selective, Antimuscarinics Related to Pirenzepine
J Med Chem 31 (6), 1169-1174, (1988)
22. Engel WW, Eberlein WG, Mihm G, Hammer R, Trummlitz G
Tricyclic Compounds as Selective Muscarinic Receptor Antagonists 3. Structure-Belectivity Relationships in a Series of Cardioselective (M₂) Antimuscarinics
J Med Chem 32 (8), 1718-1724, (1989)
23. Rudert R, Buschmann J, Luger P, Gregson D, Trummlitz G
Structure of 6-Nitro-1,2-benzisothiazol-3(2H)-one 1,1-Dioxide Sodium Salt (6-Nitrosaccharin) at 123 K based on Neutron Diffraction Data
Acta Cryst C 45, 1013 - 1015, (1989)
24. Trummlitz G, Engelhardt G, Busch U
Meloxicam
Drugs Future 14 (11) 1047-1048 (1989), update *Ibid* 15 (11) 1140 (1990), 16 (11) 1055-1056 (1991), 17 (11) 1049 (1992), 18 (11) 1083 (1993), 20 (11) 1198 (1995)
25. Engelhardt G, Trummlitz G
Biological Activity of the Main Metabolites of Meloxicam
Drugs Exp Clin Res 16 (2), 53-56 (1990)
26. Rudert R, Buschmann J, Richter T, Luger P, Trummlitz G
Electron-Density Distribution of 4-Hydroxy-1,2-benzisothiazol-3(2H)-one 1,1 Dioxide Sodium Salt (UH-AF 50 NA)
Acta Cryst B 47, 905-910 (1991)

27. Rudert R, Buschmann J, Luger P, Trummelitz G
Structures of 4-Methoxy-, 5-Chloro-, 5-Nitro- and 6-Nitro-1,2- benzisothiazol-3 (2H)-one 1,1 Dioxide Sodium Salt (4-Methoxy-, 5-Chloro-, 5-Nitro- and 6-Nitrosaccharin)
Acta Cryst B48, 269-275 (1992)
28. Daneck E, Engel W, Trummelitz G
Importance of Physico-Chemical Properties in the Activity Profile of Meloxicam
Scand J Rheumatol (Suppl 98), 113 Abstr 113 (1994)
29. Busch U, Türck D, Lehmann H, Trummelitz G
The importance of unbound plasma concentration of meloxicam for prediction of safety in various animal species in comparison to man
13 Eur Cong of Rheumatology, Amsterdam 18 – 23 Jun 1995
Rheumatol Eur 24 (Suppl 3), 188 Abstr C153 (1995)
30. Pairet M, Lidbury PS, Engelhardt G, Trummelitz G, Vane JR
Meloxicam: cyclo-oxygenase selectivity, anti-inflammatory activity and gastric renal safety
Inflamm Res 44 (Suppl 3) S 274 Abstr W15/24 (1995)
31. Schmid J, Busch U, Trummelitz G, Prox A, Kaschke S, Wachsmuth H
Meloxicam: metabolic profile and biotransformation products in the rat
Xenobiotica 25 (11), 1219-1236 (1995)
32. Luger P, Daneck K, Engel W, Trummelitz G, Wagner K
Structure and physicochemical properties of meloxicam, a new NSAID
Eur J Pharm Sci 4, 175-187 (1996)
33. Herbette L, Vecchiarelli M, Trummelitz G
NSAID mechanism of action: membrane interactions in the role of intracellular pharmacokinetics
in: Vane J, Botting J, Botting R (eds): Improved Non-steroid anti-inflammatory drugs - COX-2 enzyme inhibitors, Kluwer Academic Publishers Dordrecht/Boston/London, 85-102 (1996)
34. Pairet M, Churchill L, Trummelitz G, Engelhardt G
Differential inhibition of cyclo-oxygenase-1 (COX-1) and -2 (COX-2) by NSAIDs: consequences on anti-inflammatory activity versus gastric and renal safety
Inflammopharmacology 4 (1) 61-70 (1996)
35. Fiebich BL, Lieb K, Pairet M, Trummelitz G, Engelhardt G, Roesler N, Berger M, Gebicke-Haerter P, Bauer J
Microglia as a model of NSAID action in the brain.
Eur J Clin Pharmacol 50 (6), 541 Abstr (1996)
36. Lazer ED, Miao CK, Cywin CL, Sorcek R, Wong H-C, Meng Z, Potocki I, Hoermann M-A, Snow RJ, Tschantz MA, Kelly TA, McNeil DW, Coutts SJ, Churchill L, Graham AG, David E, Grob PM, Engel W, Meier H, Trummelitz G
Effect of structural modification of enol-carboxamide-type nonsteroidal antiinflammatory drugs on COX-2/COX-1 selectivity
J Med Chem 40 (6) 980-989 (1997)
37. Pairet M, Ryn J van, Schierok H, Mauz A, Trummelitz G, Engelhardt G

Differential inhibition of cyclooxygenases-1 and -2 by meloxicam and its 4'-isomer

Inflamm Res 47, 270-276 (1998)

38. van Ryn J, Trummelitz G, Pairet M
COX-2 Selectivity and Inflammatory Processes
Curr Med Chem 7 (11), 1145-1162 (2000)
39. van Ryn J, Pairet M, Trummelitz G
The Cyclo-Oxygenases and their Selective Inhibitions
Helix Vol X Issue 2, 3-12 (2001)
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EXHIBIT B

EXHIBIT B

Compensation

I have been retained as an expert witness on behalf of Teva Pharmaceuticals USA, Inc. in this litigation. I am compensated at a rate of \$150.00 per hour for my time spent on this matter, plus expenses.

Prior Testimony

In the last four years I have not testified.

EXHIBIT C

EXHIBIT C

MATERIALS REVIEWED

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41. Teva Exhibits:

| | | |
|-----|------|-----|
| 8 | 12 | 29 |
| 33 | 40 | 51 |
| 52 | 68 | 146 |
| 150 | 151 | 152 |
| 186 | 234A | 241 |
| 244 | | |

42. Deposition Transcripts:

| | |
|---------|-----------|
| Bullock | Carter |
| Collins | Docter |
| Graneto | Khanna |
| Koboldt | Miyashiro |
| Penning | Talley |

43. Pfizer's Responses to Defendant Teva Pharmaceutical USA, Inc.'s Third Set of Requests for Admission.

44. Plaintiffs' Documents (PFC):

| | | |
|---------|---------|--------------|
| 290246 | 650448 | 00655886-907 |
| 1204063 | 1554541 | 1554559 |
| 1554608 | 1554613 | 1554631 |
| 1554656 | 1554690 | 1555109 |
| 1555132 | 1555146 | 1555162 |
| 1555190 | 1555218 | 1555246 |
| 1555278 | 1555294 | 1555314 |

EXHIBIT B

Compensation

I have been retained as an expert witness on behalf of Teva Pharmaceuticals USA, Inc. in this litigation. I am compensated at a rate of \$150.00 per hour for my time spent on this matter, plus expenses.

Prior Testimony

In the last four years I have not testified.

CERTIFICATE OF SERVICE

I hereby certify that I caused a true and correct copy of the foregoing Expert Report of Guenter Trummnitz, Ph.D. to be served by electronic mail on the 5th day of May 2006 on the counsel for the defendant as follows:

Daniel L. Reisner, Esq.
Kaye Scholer LLP
425 Park Avenue
New York, NY 10022-3598
Fax: 212-836-8000

I hereby certify that I caused a true and correct copy of the foregoing Expert Report of Guenter Trummnitz, Ph.D. to be served by first class mail on the 5th day of May 2006 on the counsel for the defendant as follows:

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